Impact of Prior Nicotine Replacement Therapy on Smoking Cessation Efficacy

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***Objective*: To examine previous use of nicotine replacement therapy (NRT) on the smoking-cessation efficacy of bupropion sustained release (SR). *Methods*: Secondary analysis of a parallel-group, randomized, double-blind, placebo-controlled study. Smokers who had, based on self-report, no previous history of NRT (N=453) or who had used NRT at least once (N=440) were randomized to receive placebo, bupropion SR, nicotine transdermal system (NTS), or a combination of bupropion SR and NTS. *Results*: Bupropion SR showed similar efficacy in participants with or without previous use of NRT. *Conclusion*: Bupropion SR is effective in promoting smoking abstinence regardless of prior NRT use.**

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Between 1991 and 1994, more than 4 million smokers in the United States received prescriptions for the nicotine patch.[1] With the subsequent availability of these medications as over-the-counter products, their use has become increasingly widespread.[2] However, approximately 4 out of 5 users of these products will relapse within 6 months of stopping smoking,[1] and on average each smoker will make 5 to 7 serious attempts before they are successful.[3] Many smokers who are embarking on a smoking-cessation program will therefore have tried nicotine replacement therapy (NRT) previously. Thus the impact of previous attempts to stop smoking on the outcome of future attempts is a major consideration in any smoking-cessation program.

In this report, a retrospective analysis of the effect of previous use of NRT on the efficacy of bupropion sustained release (bupropion SR, Zyban™) is described. The efficacy of bupropion SR alone and in combination with a nicotine transdermal system (NTS, Habitrol™) is compared in participants who have no previous history of NRT use and participants who have made at least one previous attempt to stop smoking using NRT. This *post hoc* analysis describes the effect of prior history of NRT use on quit rates at and closely after the end of treatment. This time frame was chosen because bupropion SR was originally approved as an aid to smoking-

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A history of any previous treatment with bupropion was a criterion for exclusion.

cessation based on patients' remaining continuously abstinent for the 4-week period prior to the end of treatment (Days 22 through 49: Zyban Prescribing Information, GlaxoWellcome Inc 1997). A similar "4-week quit rate" has been used for the regulatory approval of nicotine replacement products. The purpose of this *post hoc* analysis was to assess whether prior history of NRT usage influenced this outcome measure.

METHODS

Participants

To be eligible for enrollment, adult participants were required to have smoked at least 15 cigarettes/day throughout the previous year and be motivated to stop. Participants were excluded if they were predisposed to seizure or had a history or current diagnosis of anorexia nervosa or bulimia or severe renal, hepatic, neurological, or chronic pulmonary disease. Participants were also excluded if they had a history of peptic ulcer or any unstable cardiovascular disease including history of myocardial infarction medical condition.

A history of any previous treatment with bupropion was also criterion for exclusion. However, with regard to NRT, only the use of NRT within the past 6 months was excluded. Therefore a number of patients included in the study had a prior history of NRT use. Prior use of NRT was captured in answer to the question "What methods have you used in previous attempts to stop smoking?" The choices in answer to this question were "Not applicable (have never tried to stop smoking before)"; "Nicotine Gum (Nicorette)"; "On my own (ie, cold turkey)"; "Clonidine (Catapres)"; "Group sessions"; "Hypnotism"; "Acupuncture"; or "Nicotine patches". Participants were asked to check all that applied to them. Participants with a history of NRT were defined as those participants reporting one or more previous experiences with NRT, ie, those reporting that they had previously used either nicotine gum or nicotine patches in previous quit attempts. Those patients who reported no prior use of an NRT product were defined as having no history of NRT use. The study was performed in compliance with institutional review board regulations and in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study Design

This was a secondary analysis of a 4-center, parallel-group, randomized, double-blind, placebo-controlled study consisting of a 1-week baseline phase, a 7-week treatment phase, a 2-week taper phase, and a 1-week follow-up.

Prior to randomization, participants completed a smoking-history questionnaire that documented the number of cigarettes smoked, the number of serious attempts to stop smoking, and the methods used in previous attempts. Participants underwent an assessment of nicotine dependence with the Fagerström Tolerance Questionnaire, and serum cotinine levels were also measured. The randomization code for this study used a block size of 11. Within each block of 11, two patients were assigned to the placebo group, and 3 patients were assigned to each of the bupropion SR (150 mg b.i.d.), NTS (21 mg/day, Habitrol™, Novartis Consumer Health.) or bupropion SR in combination with NTS (bupropion SR/NTS). A double-dummy design was used; therefore, each patient received tablets (either active or placebo) and a transdermal system (either active or placebo).

Bupropion SR, or matching placebo, was initiated one week before the target quit date (TQD) and continued until the end of the treatment phase (150 mg q.d. days 1-3; 150 mg b.i.d. days 4-49). The TQD was typically Day 8; however, patients were given the flexibility to choose a quit date that was suitable for them, and thus there is variability in the TQD in relation to the start of treatment, and not all patients used Day 8 as the TQD. Participants were instructed not to attempt to stop smoking before their TQD and not to apply the transdermal patch until their TQD. At the Week-1 (Day-7) clinic visit and at each subsequent weekly visit, participants were provided with

transdermal patches (21 mg nicotine or placebo). Beginning on the morning of the TQD, participants were instructed to apply a single patch to their trunk or the upper, outer portion of one arm. Patches were to be worn for 24 hours each day from the TQD through Day 49 (Week 7). During this treatment phase, participants made weekly clinic visits at which brief supportive counselling was provided and exhaled carbon monoxide (CO) levels were measured using Smokerlyzer™ monitors (Bedfont Scientific, USA). Participants who were unsuccessful in adhering to their TQD were encouraged to set a new TQD at each clinic visit as necessary.

Participants who completed the 7-week treatment phase entered a 2-week taper phase. Participants received progressively lower-dose transdermal patch during weeks 8 (14 mg or placebo) and 9 (7 mg or placebo) and continued to receive bupropion SR, or matching placebo. Daily diaries were used by participants to record the number of cigarettes smoked throughout the treatment and taper phases. Study personnel queried participants if discrepancies existed between the verbal response during the clinic visit, the reports in the daily diary, or exhaled CO levels. Finally there was a 1-week follow-up phase during which no study medication was taken.

Outcomes

The primary efficacy outcome in this analysis was continuous abstinence from smoking. Continuous quit rates were determined for participants who remained continuously abstinent through each 7-day period. Continuous quit rates were expressed as the percentage of participants who were continuously abstinent since Day 22. Continuous abstinence from Day 22, rather than TQD, was used because of the variability in the TQDs chosen by the patients; additionally, this enabled patients who failed on their initial quit to try again. Therefore, it was possible for a patient to have more than one TQD between Days 8 and 21; if TQD was used as the start date in this instance, it would not be clear which of these TQDs to use. However, in order to demonstrate 4 weeks of successful continuous abstinence prior to the end of Week 7, they would have to have quit prior to Day 22. Continuous abstinence from smoking was defined as a patient report of no smoking (ie, 0 cigarettes / day, not even a single puff) confirmed by exhaled air CO levels of =10ppm at weekly clinic visits. Participants were considered abstinent up to the last week for which a confirmatory CO level was obtained. This analysis was carried out to identify whether any differences existed between participants with and without previous experience with NRT.

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Analyses

Treatment comparisons were made using 2-sided tests and confidence intervals with an a level of significance of 0.05. P values less than 0.05 were considered to be statistically significant. Between-treatment-group comparisons were made using analysis of variance for continuous variables and Cochran-Mantel Haenzel chi-squared test for categorical variables.

RESULTS

At the start of the study, 1,182 participants entered the screen phase of whom 289 failed to meet the criteria for randomization. Therefore, 893 participants were randomized to treatment (placebo 160, bupropion SR 244, NTS 244, bupropion SR/NTS 245). The mean age of the participants was 43.3 years, and 52% were female. They had smoked an average of 27 cigarettes each day during the previous year and had a mean smoking duration of 26 years (Table 1).

Throughout the treatment, taper, and follow-up phases, the levels of continuous abstinence were significantly greater in participants receiving bupropion SR, NTS, and bupropion SR/NTS when compared with placebo ($p<0.05$ at all time points; Figure 1). Participants receiving bupropion SR both alone and in combination with NTS also showed significantly greater levels of continuous abstinence when compared with the use of NTS alone

TABLE 1
Characteristics of Participants With and Without (W/O) Previous Use of NRT

	Placebo		Bup SR		Patch		Bup SR & Patch		All Treatments	
	NRT	W/O NRT	NRT	W/O NRT	NRT	W/O NRT	NRT	W/O NRT	NRT	W/O NRT
Age[a]	43.2±9.2	42.1±11.3	44.9±9.1	39.6±10.7	45.3±10.6	42.8±11.1	46.1±10.5	41.9±12.2	45.0±9.9	41.6±11.4*
Female (%)	53 (61)	41 (56)	67 (54)	59 (49)	59 (52)	67 (52)	63 (54)	58 (45)	242 (55)	225 (50)
White (%)	81 (94)	68 (93)	116 (95)	113 (96)	108 (96)	119 (92)	107 (95)	119 (94)	412 (95)	419 (94)
Fagerström Score[a]	7.4±1.9	7.5±1.6	7.4±1.6	7.5±1.5	7.6±1.6	7.1±1.8	7.3±1.8	7.2±1.8	7.4±1.7	7.3±1.7
CPD in last year[a]	28.2±10.0	28.0±11.3	25.9±9.9	25.7±7.5	28.1±10.2	25.2±8.3	27.0±8.9	26.6±9.9	27.2±9.7	26.0±9.2
Years smoked[a]	26.5±8.9	24.6±11.0	27.0±9.4	22.2±11.1	28.6±10.4	25.3±11.5	28.9±10.6	24.8±12.1	27.8±9.9	24.2±11.5*
Attempts to stop[a]	3.9±3.3	1.5±1.7	3.5±3.3	2.7±5.8	3.5±2.5	2.0±2.1	3.0±2.0	2.0±2.7	3.5±2.8	2.1±3.6*
Serum cotinine (ng/ml)	358±168	355±143	369±181	344±158	397±236	349±167	370±176	353±156	374±194	350±157

* **Indicates significant difference from participants with history of NRT ($p<0.05$). Cigarettes per day (CPD).**
a **(n±SD)**

($p<0.05$, weeks 4-10; Figure 1).

Secondary Analysis According to Previous Experience with NRT

Of the 893 participants randomized to treatment, 453 (51%) reported no prior experience with NRT, and 440 (49%) reported that they had made at least one previous attempt to stop smoking with the aid of NRT.

Continuous Abstinence in Participants Who Previously Used NRT

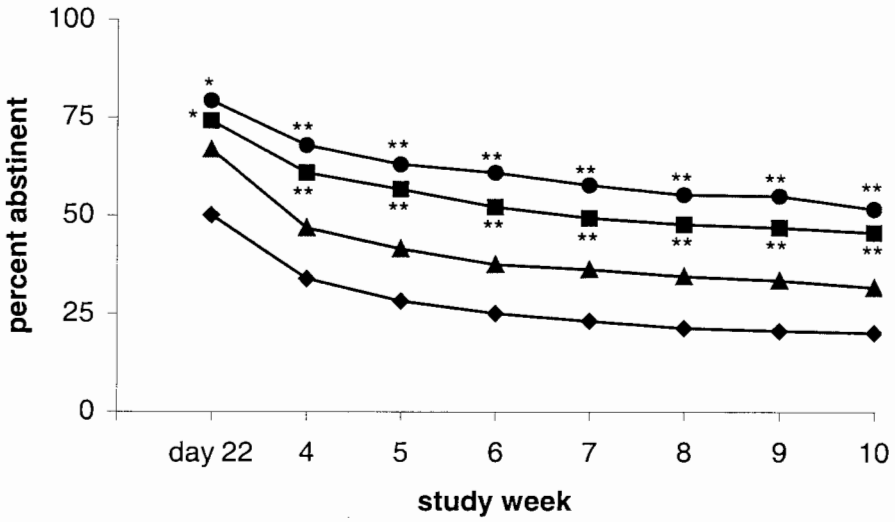
Four hundred forty participants who had previously attempted to stop smoking using NRT were randomized to treatment (placebo=87, bupropion SR=123, NTS=114, bupropion SR/NTS=116). These participants had a mean age of 45 years, and 55% were female. They had smoked a mean of 27 cigarettes / day for the previous year and had been smoking for an average of 28 years. The mean number of previous attempts to stop smoking was 3.5, and the mean serum cotinine concentration was 375ng/ml at baseline. The mean Fagerström Tolerance score was 7.4 ± 1.7 (Table 1).

In participants who had previously attempted to stop smoking using NRT, 46% (40/87) receiving placebo, 71% (88/123) receiving bupropion SR, 69% (79/114) receiving NTS, and 83% (97/116) receiving bupropion SR/NTS were abstinent at Day 22. Throughout the treatment, taper, and follow-up phases, bupropion SR alone or in combination with NTS resulted in a significant improvement in the levels of continuous abstinence when compared with either NTS alone or placebo ($p<0.05$ at all time points; Figure 2). In addition, NTS alone resulted in significantly improved levels of continuous abstinence compared to placebo ($p<0.05$ at all time points; Figure 2).

Continuous Abstinence in Participants with No Experience with NRT

Four hundred fifty-three participants with no previous experience with NRT were randomized to treatment (placebo=73, bupropion SR=121, NTS=130, bupropion SR/NTS=129). These participants were a mean of 42 years of age, and

Figure 1
The Effect of Bupropion SR, NTS, Combination of Bupropion SR/NTS, and Placebo on Levels of Continuous Abstinence in All Participants Who Were Abstinent from Smoking at Day 22



■ Bupropion SR
▲ Nicotine transdermal system (NTS)
● Bupropion SR/NTS
♦ Placebo
* Indicates p<0.05 when compared to placebo
** Indicates p<0.05 when compared with NTS and placebo

50% were female. They had smoked a mean of 26 cigarettes / day during the previous year and had smoked for a mean of 24 years. They had attempted to stop smoking a mean of 2.1 times previously and had mean cotinine levels of 350ng/ml at baseline. The mean Fagerström Tolerance score was 7.3±1.7 (Table 1).

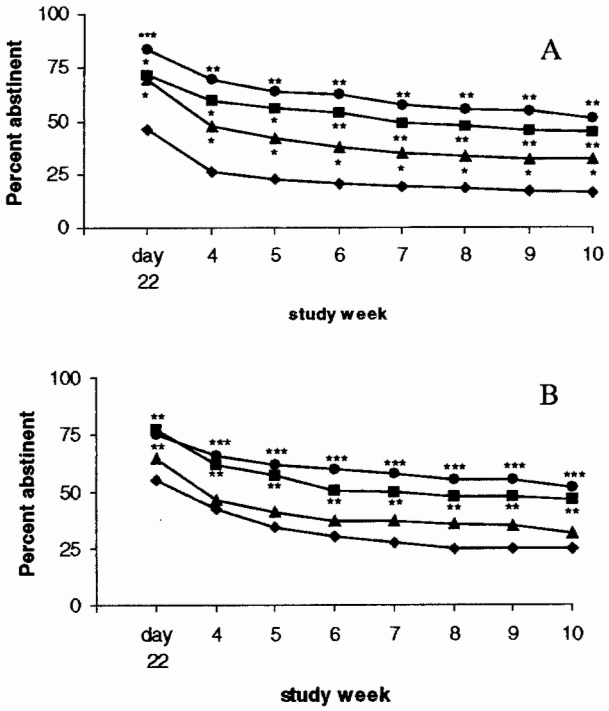
In participants who had not previously attempted to stop smoking using NRT, 55% (40/73) receiving placebo, 77% (93/121) receiving bupropion SR, 65% (84/130) receiving NTS, and 75% (97/129) receiving bupropion SR/NTS were abstinent at Day 22. Throughout the treatment, taper, and follow-up phases bupropion SR either alone or in combination with the NTS resulted in significantly improved levels of continuous abstinence compared with NTS alone or with placebo ($p<0.05$ at all timepoints; Figure 2). The use of the NTS alone did not result in a significant improvement in the levels of abstinence compared with placebo ($p>0.05$ at all time points; Figure 2).

Comparison of Participants With and Without Previous Experience of NRT

Participants with a history of NRT were statistically significantly older (about 4-5 years), had smoked for longer (3-4 years), and had made 1 or 2 more previous attempts to stop smoking ($p<0.05$ in each case) than had participants who had never attempted to stop smoking using NRT (Table 1).

Previous use of NRT did not have a significant effect on the efficacy of bupropion SR, NTS or a combination of the 2 therapies ($p>0.05$ for all time points). At Week 10, 52% of participants with no history of NRT who were receiving bupropion SR/NTS remained abstinent. Similarly, 51% of participants who had

Figure 2
The Effect of Bupropion SR, NTS, Combination of Bupropion SR/NTS, and Placebo on Levels of Continuous Abstinence in Smokers With (A) and Without (B) a Prior History of NRT



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* Indicates p<0.05 when compared to placebo
** Indicates p<0.05 when compared with NTS and placebo
*** Indicates p<0.05 when compared with NTS alone, bupropion SR alone, or placebo

previously used NRT and who were receiving bupropion SR/NTS remained abstinent. The Week-10 levels of abstinence were also similar for treatment with bupropion alone (previous NRT 45% abstinent; no previous NRT 46% abstinent) and NTS alone (previous NRT 32% abstinent; no previous NRT 32% abstinent). Placebo response rates were higher in participants with no history of NRT compared with participants who had previously used NRT. This difference was statistically significant at Week 4 during the treatment phase (NRT 26.4%, no NRT 42.5%; p<0.05).

Safety and Tolerability

All treatments were generally well tolerated. Complete safety data from the present study have been published previously.[4]

DISCUSSION

Only 3% of people who stop smoking unaided will remain completely abstinent after 6 months.[5] The use of NRT increases the likelihood of continued abstinence although the rates of relapse are still high.[1] It is therefore important to

understand the impact of treatments used in previous failures on subsequent attempts to stop smoking. In the present study, previous use of NRT, which did not secure the complete abstinence from smoking, had little or no impact on the success of subsequent smoking-cessation attempts with bupropion SR. Bupropion SR both alone and in combination with NTS significantly improved levels of continuous abstinence in participants with and without a previous history of NRT use compared with placebo. There were no clinically significant differences in rates of continuous abstinence between participants with or without a previous history of NRT in each of the treatment groups.

The primary outcome from the present study has been published previously.[4] Bupropion SR either alone or in combination with the nicotine patch is effective in promoting abstinence from smoking. The rates of continuous abstinence seen with bupropion SR either alone or with a nicotine patch are significantly different from those of either nicotine patch alone or placebo.

In the present study, participants with a history of NRT use were significantly older, had smoked longer, and had on average made more previous attempts to stop smoking than had those who had not used NRT. However, although statistically significant, the differences in these parameters were numerically small and are unlikely to be of clinical significance. At baseline, participants were stratified according to their previous use of NRT; by definition all participants with previous use of NRT had made at least one previous attempt to stop smoking. Thus, the group of patients with a history of previous NRT use would be expected to have more previous quit attempts than would those without a previous history, because this group cannot contain patients with zero quit attempts. It therefore follows that smokers who have made more attempts to stop smoking are likely to have smoked for longer and be generally older. Thus the criteria for stratification in the present study are responsible for these minor differences seen in the participant populations.

In the present study we found that NTS was significantly superior to placebo in participants with a history of NRT, but in NRT-naïve participants, the difference between placebo and NTS did not reach statistical significance. Placebo response rates were slightly higher in participants with no history of NRT compared to participants with a history of NRT, thus diminishing the absolute difference between NTS and placebo in this subgroup. This, accompanied by the decreased statistical power resulting from the division of the total population into 2 subgroups (ie, those with, and those without prior experience with NRT), is the explanation for the failure to achieve statistical significance.

...in this study all patients did receive brief behavioral counseling...

The levels of abstinence that are achieved with use of nicotine patches decrease with repeated courses of treatment. Following a placebo-controlled trial with nicotine patches,[6] participants who relapsed to heavy smoking were recruited to a follow-up open-label study also using the nicotine patch.[7] Higher rates of abstinence were found in those participants who received placebo in the initial study compared with those who received active patch therapy (NRT in initial trial=0%, placebo in initial trial=12% after 26 weeks). Another series of trials[8,9] indicated that levels of abstinence may be reduced by up to 70% when using a second course of NRT. In the current analysis however, previous experience with NRT did not seem to substantially influence the efficacy of treatment with NTS. In this study patients were not recruited on the basis of a previous failure, and other than asking if they had previously used NRT, nothing was discussed with the patients regarding previous failures. The patients may have therefore been able to maintain a higher level of motivation due to the fact that attention was not drawn to a previous failure. However, it also remains possible that the lack of success in achieving permanent abstinence on previous attempts with NRT may have been due to an inappropriate use of the product (eg, poor compliance or discontinuing therapy too early). Additionally, in this

study all patients did receive brief behavioral counseling; it is possible that for some patients who had used NRT previously and were not successful, there had been insufficient access to appropriate counseling. It is also important to note that this analysis is based on prior experience with NRT and not whether the participants felt their prior experience was a success or failure. There may have been many participants who felt they had had a successful quit attempt with NRT but subsequently returned to smoking. In order to qualify for the current trial, participants had to be smoking at least 15 cigarettes per day; therefore, the prior use of NRT had not resulted in a permanent abstinence from smoking. The participant's opinion as to the success or failure of their previous quit attempts was not formally probed.

Because the data presented here are from a *post hoc* analysis of a study designed to assess smoking-cessation *per se* (ie, without regard to the presence or absence of previous experiences), it is important to be aware of its shortcomings. This study was not designed or powered to detect differences based on previous treatment; however, the current analysis would suggest that if any such effects exist, they would appear to be very slight, and therefore a much larger study would be required to detect them. Becoming an ex-smoker involves both an initial cessation followed by a long-term maintenance of abstinence. The current analysis focuses on the former. It is likely that many factors, in addition to the short-term efficacy of pharmacological treatment, influence the latter such as the management of risk factors that might trigger relapse. The influence of those factors was beyond the scope of the analysis presented here. A fuller understanding of factors involved in maintaining long-term abstinence following an initial cessation merits further systematic study.

As NRT becomes more widespread, increasing numbers of smokers will have made previous attempts to stop smoking using nicotine replacement. Simple retreatment of transdermal therapy failures with the same medication has been reported to have limited success.[3] Treatment with bupropion SR results in improved continuous abstinence in smokers with and without previous use of NRT compared to placebo and NTS. Bupropion SR with or without NRT is a viable option for use in smoking-cessation programs irrespective of the previous use of nicotine replacement therapy. It is important that the smoker and the health care professional work together to maximize the chances of making the first attempt to quit a lasting success.

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